Original Contribution

Prostate Cancer and Ambient Pesticide Exposure in Agriculturally Intensive Areas in California

Myles Cockburn*, Paul Mills, Xinbo Zhang, John Zadnick, Dan Goldberg, and Beate Ritz

* Correspondence to Dr. Myles Cockburn, Department of Preventive Medicine, Keck School of Medicine, University of Southern California, 1441 Eastlake Avenue, MC 9175, Los Angeles, CA 90089-9175 (e-mail: mylesc@usc.edu).

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In a population-based case-control study in California's intensely agricultural Central Valley (2005–2006), the authors investigated relations between environmental pesticide/fungicide exposure and prostate cancer. Cases (n=173) were obtained from a population-based cancer registry, and controls (n=162) were obtained from Medicare listings and tax assessor mailings. Past ambient exposures to pesticides/fungicides were derived from residential history and independently recorded pesticide and land-use data, using a novel geographic information systems approach. In comparison with unexposed persons, increased risks of prostate cancer were observed among persons exposed to compounds which may have prostate-specific biologic effects (methyl bromide (odds ratio = 1.62, 95% confidence interval: 1.02, 2.59) and a group of organochlorines (odds ratio = 1.64, 95% confidence interval: 1.02, 2.63)) but not among those exposed to other compounds that were included as controls (simazine, maneb, and paraquat dichloride). The authors assessed the possibility of selection bias due to less-than-100% enrollment of eligible cases and controls (a critical methodological concern in studies of this kind) and determined that there was little evidence of bias affecting the estimated effect size. This study provides evidence of an association between prostate cancer and ambient pesticide exposures in and around homes in intensely agricultural areas. The associations appear specific to compounds with a plausible biologic role in prostate carcinogenesis.

fungicides, industrial; hydrocarbons, brominated; pesticides; prostatic neoplasms; selection bias

Abbreviations: CI, confidence interval; DDE, dichlorodiphenyldichloroethane; GIS, geographic information systems; OR, odds ratio; PLSS, Public Land Survey System; PUR, Pesticide Use Reports.

There are few established risk factors for prostate cancer, and the search for plausible environmental causes is under way. Prostate cancer incidence rates after age 45 years increase at a rate approaching the ninth power of age (1), which is compatible with an accumulated environmental exposure, such as long-term exposure to occupational or environment toxins interfering with normal hormone function (2), and with genetic differences in susceptibility (3). Variations in hormone levels affect prostate cancer risk, since normal growth of the prostate gland is dependent on a critical balance of androgen (sex hormone) levels (4). A variety of pesticides have the ability to affect hormone functioning by mimicking hormones, affecting enzyme systems involved in hormone metabolism, or directly affecting the brain regions

involved in hormone functioning (5, 6). Furthermore, certain pesticides may affect androgenic stimulation of the prostate, potentially leading to cell proliferation and cancer (7).

The pesticide methyl bromide exhibits genotoxic potential (8). Studies in rats and mice (9, 10) indicate that methyl bromide is an alkylating agent in which the methyl group covalently binds to DNA, creating DNA adducts, O^6 - and N^7 -methylguanine (9, 11). O^6 -methylguanine is a directly miscoding lesion capable of pairing with both cytosine (the correct nucleotide) and thymine (the incorrect nucleotide) during DNA replication, resulting in a G:C to A:T transition mutation (12, 13). These gene mutations may represent the early steps in prostate carcinogenesis. Some organochlorine pesticides induce overexpression of an oncogene implicated

in prostate cancer (erbB-2), which in turn produces cell proliferation in prostate cancer cells (14).

Various farming occupations have high rates of prostate cancer (15). In a recent case-control study carried out in the United Farm Workers of America cohort, Mills and Yang (16) derived pesticide exposure information by cross-linking county-, crop-, month-, and year-specific work histories from union records with similar county-, crop-, month-, and year-specific Pesticide Use Reports (PUR) from the California Department of Pesticide Regulation. Associations were found between prostate cancer and a group of organochlorine pesticides, and there was a weak association with methyl bromide (16). The fungicide captan has also been shown to be related to prostate cancer incidence in California farm workers (17).

Although, in a recent meta-analysis, Parent and Siemiatycki (7) reported a weak summary relative risk of 1.1 for the relation between farming and prostate cancer, a majority of studies with a sufficiently large number of subjects have shown excess relative risks of prostate cancer ranging from 1.06 to 5.0 among farmers, farm laborers, pesticide manufacturers, and pesticide applicators (5, 18), and a strong case can be made for the biologic plausibility of an effect of specific pesticides (such as some organochlorines and methyl bromide) on prostate cancer, especially in agriculturally intense areas such as California's Central Valley. The majority of studies conducted to date have relied on self-reports of pesticide exposure or on exposure data based broadly on occupation; as a result, many investigators' failure to find associations may have been due to exposure misclassification, biasing effects towards the null (19).

Much current evidence regarding the role of pesticide exposure in prostate cancer focuses on occupational exposures not representative of those experienced by the general population (15, 20–22). In this report, we focus on objective estimates of residential exposure to pesticides in the environment ("ambient exposure") from drift or contaminated soil/dust (19, 23-25) and their impact on prostate cancer in a population-based case-control study. We studied the impact of 3 select compounds with a biologically plausible link to prostate cancer (i.e., methyl bromide, a group of organochlorines (dicofol, dieldrin, dienochlor, endosulfan, heptachlor, lindane, methoxychlor, and toxaphene), and captan) and 3 compounds that are commonly used in the Central Valley but have no specific link to prostate cancer (simazine, maneb, and paraquat dichloride), to help rule out the possibility that some factor associated in general with pesticide exposures was responsible for increased risk.

Because previous studies may have been limited by their study designs, we attempted to address 2 major and important potential biases by 1) improving exposure assessment methods and 2) assessing the potential impact of selection bias on risk estimates for pesticide exposure in a novel manner.

MATERIALS AND METHODS

Selection of cases and controls

We identified all patients aged 60–74 years diagnosed with histologically confirmed prostate cancer between August

2005 and July 2006 in Tulare, Fresno, and Kern counties (California) from the records of the California Cancer Registry. Only non-Latino whites and Latino whites were included; prostate cancer in other racial/ethnic groups was too rare for inclusion (either because of the low rate of prostate cancer in most other groups or, as in the case of African Americans, because they represented small populations in the Central Valley). The Registry provided cases' addresses and telephone numbers, which were used for recruitment, and whenever these were unusable, we traced patients using marketing company services to obtain updated contact information.

Control subject recruitment, described elsewhere (26), was from a study of Parkinson's disease being conducted in the same study area. Controls aged 65 years or more were identified from Medicare lists in 2001 and were mailed recruitment materials, but because of implementation of the Health Insurance Portability and Accountability Act, which prohibited the continued use of Medicare enrollees, additional controls were recruited from randomly selected tax assessor residential units (parcels) in each of the 3 counties. Controls were recruited between 2004 and 2006. We mailed recruitment materials to a random selection of residential units and also attempted to identify head-ofhousehold names and telephone numbers for these parcels using the services of marketing companies and Internet searches. Eligibility criteria for the Parkinson's disease study controls were: 1) not having Parkinson's disease or prostate cancer and 2) being at least 60 years of age. Additional eligibility criteria for both cases and controls were: 1) currently residing primarily in one of the 3 study counties and 2) having lived in California for at least 5 years prior to the study.

Source of exposure data

Recruited cases and controls were mailed an informed consent document, a timeline of important world events, a blank 1900–2005 calendar (to aid in recalling residential history), and a job history questionnaire, all to be completed prior to interview. A comprehensive risk factor interview was conducted by telephone and obtained demographic information (age (in years), race/ethnicity (non-Latino white or Latino white), and birthplace (city and state in the United States or city and country outside the United States)). We obtained detailed information on residential history, including dates of residence, address information, and local landmarks, for the purpose of determining ambient pesticide exposures.

Assessment of ambient pesticide exposure

Age-specific ambient pesticide exposures and exposures occurring between 1974 and 1999 were determined using methods previously described (19, 26, 27). Briefly, California PUR data regarding the application of pesticides were combined with data from land-use surveys (based on California's Public Land Survey System (PLSS), specifying the exact location of specific crops on which those pesticides were most likely used) to determine the geography of pesticide

use between 1974 and 1999. Historical residential locations between 1974 and 1999 were then used to determine potential pesticide exposure for an individual's residential time and place by summing data on pesticide use within a 500-m buffer around the dwelling.

The California PUR form documents, for each pesticide application, the name of the pesticide's active ingredient, the number of pounds of pesticide applied, the crop and acreage of the field, the application method, and the date and location of the application. We calculated annual application rates (total pounds applied per acre in a PLSS section) for all polygons linked to the PUR data, using an algorithm developed and validated previously (19). When a PUR matched exactly to land-use polygons in a PLSS section by crop type, both records were directly linked. If pesticide use was reported on a crop that did not match any of the crops listed in the land-use survey in a PLSS section, yet the section contained other field, vineyard, or orchard crops, we assumed that these crop locations were possible sites where the reported crop had been grown. Finally, if a PUR matched a PLSS section but, according to the land-use survey, no field, vineyard, or orchard crops were present in the section, we assumed that any area within the entire section could have been treated (19).

All historical residential addresses supplied by cases and controls were geocoded to obtain a latitude and longitude. Exposure misclassification due to the exclusion of locations that were not geocodeable was a concern (28). We used manual resolution methods to pinpoint locations that could not be geocoded automatically, as detailed elsewhere (29). Briefly, for every address, we obtained information on landmarks and surrounding geographic features to aid in the manual resolution of nonstandard addresses to a latitude/longitude. We recorded the "accuracy" of geocoding in every case. Sensitivity analyses specific to various levels of geocoding accuracy did not alter any of the results presented herein.

Measurement of other pesticide exposures

While we collected detailed information on home use of pesticides and occupational pesticide use, for the purposes of this analysis we considered self-reports of home pesticide use as representing "ever" or "never" use. For occupational exposures, which were assessed by means of a job exposure matrix approach according to job titles and tasks, we used the method outlined in the article by Young et al. (30) to define 3 exposure levels: "probably exposed to pesticides" ("intensity" ≥ 0.3 in the paper by Young et al. (30)); "possibly exposed" (0 < "intensity" < 0.3); and "not exposed" ("intensity" = 0). The "intensity" of exposure reflects the likelihood of exposure to pesticides/herbicides based on self-reported occupation, weighted by usual exposures experienced by persons in those occupations (30).

Selection of pesticides for analysis

We focused in this study on those chemicals thought most likely to be related to prostate carcinogenesis (methyl bromide, the group of organochlorines (dicofol, dieldrin, dienochlor, endosulfan, heptachlor, lindane, methoxychlor, and toxaphene), and captan). As control exposures, we selected 3 chemicals that are widely used in the 3-county study area and have similar geographic distributions as each of the 3 potential prostate carcinogens yet are unlikely to produce prostate-specific carcinogenic effects (paraquat dichloride, simazine, and maneb).

Statistical analysis

We calculated odds ratios and 95% confidence intervals to assess associations between specific pesticide exposures and prostate cancer using unconditional logistic regression in SAS 9.1.3 (SAS Institute, Inc., Cary, North Carolina). We considered residential exposure for the period 1974–1999, which is the time frame represented by complete PUR and land-use data in our geographic information systems (GIS) model, by summing all exposure values weighted by the number of years of exposure. To assess the potential impact of a lag between exposure and the development of disease, we separately calculated exposures accumulated until 15 years before diagnosis and until 10 years before diagnosis. In all cases, for years with missing exposures we imputed exposure using the time-weighted average approach, which imputes missing data with the average of the data from nonmissing years for the same individual (31). Sources of missing exposure data included missing residential information, unusable residential information, and residence outside the 3-county study area.

Odds ratios were calculated comparing "any exposure" with "no exposure," and also by comparing "low" and "high" exposures with "no exposure" to address possible exposure-response. "Low" and "high" exposure cutpoints were based on the median of the distribution of exposures to each pesticide (pesticide group, in the case of organochlorines) in control subjects. We adjusted these odds ratios for age (continuous), race/ethnicity (Latino white, non-Latino white), self-reported home pesticide use (ever/never), and occupational pesticide exposures derived from the job exposure matrix (not exposed, possibly exposed, or probably exposed, as detailed above). No other variables from our extensive risk factor questionnaire (e.g., body mass index and crude food frequency items) were implicated in univariate analyses (data not shown), so none were included in the final models.

Assessment of selection bias in cases and controls

We estimated the impact of sample selection/participation bias on pesticide exposures by calculating pesticide exposures for all originally selected cases (n=670) and all originally selected controls (n=1,212) and comparing those exposures to exposures among participating cases (n=173) and controls (n=162). Little was known about prostate cancer risk factors among the cases who did not respond to the study invitation (other than the details provided in Table 1), and nothing was known about nonresponding controls. However, residential locations at recruitment (diagnosis address for Registry cases and residential tax assessor parcel for all selected control locations, including those selected from Medicare address listings) were known.

Table 1. Characteristics of Surveyed Prostate Cancer Cases and Cases Selected From the Population-based California Cancer Registry, California's Central Valley, 2005-2006

Characteristic	Selecte	ed Cases	Surveyed Cases	
Characteristic	No.	%	No.	%
Age at diagnosis, years				
60–64	151	26.8	51	29.5
65–69	215	38.2	66	38.2
70–74	197	35.0	56	32.4
Tumor stage				
Localized	460	81.7	145	83.8
Regional, distant, or missing data	103	18.3	28	16.2
Birthplace				
United States	230	40.9	79	45.7
Other country	70	12.4	25	14.5
Missing data	263	46.7	69	39.9
Race/ethnicity				
Non-Latino white	337	59.9	126	72.8
Latino white	226	40.1	47	27.2
Total	563	100	173	100

Therefore, pesticide exposures were generated for the 1974– 1999 time period (using the methods described above) for all originally selected cases (n = 670) solely on the basis of their diagnosis address and for all tax assessor parcel centroids for the population of potential control subjects (n = 1,212). The odds ratios for the selected cases and controls could be considered population-based estimates, which are not affected by respondent participation bias. Comparable odds ratios were also calculated for those cases and controls participating in the study based on their residential diagnosis/contact address only. Note that these odds ratios do not match the main results we have presented here, because the bias analysis results are based on 1974-1999 PUR data referenced only to a single address at diagnosis/contact rather than a true residential history from this period, and we had no additional risk factor data with which to adjust these estimates. Finally, we compared participating cases with all those reported to the Registry during the same time period, by stage at diagnosis, birthplace, age, and race/ethnicity—all obtained from Registry records.

The institutional review boards of the participating institutions approved this study.

RESULTS

Participating cases and controls

We attempted to contact 563 of the 640 eligible cases before the study ended. The response rate among cases was 30.7%, and after removing 112 cases who had no valid contact information, 37.9%. The only notable difference between the originally selected and analyzed cases was that 73% of the analyzed cases were non-Hispanic white as compared with only 60% of the underlying Registry cases (Table 1). All subsequent analyses were controlled for

Table 2. Characteristics of Prostate Cancer Cases and Control Subjects, California's Central Valley, 2005-2006

Variable	Cas (n =		Controls (n = 162)	
	No.	%	No.	%
Age group, years				
60–64	51	29	46	28
65–69	66	38	37	23
70–74	56	32	79	49
Race/ethnicity				
Non-Latino white	126	73	124	77
Latino white	47	27	38	23
Occupational pesticide use				
Missing data	3	2	0	0
Not exposed	97	56	105	65
Possibly exposed	9	5	8	5
Probably exposed	64	37	49	30
Home pesticide use ^a				
Exposed	160	92	147	91
Not exposed	13	8	15	9

^a Self-reported use of pesticides around the home, as defined in the text.

race/ethnicity. We conducted analyses stratified by stage of disease (localized vs. regional, distant, and unknown combined), and the results were similar to those presented below.

For the Parkinson's disease study (26), the source of control subjects, we successfully contacted 1,212 potential controls by mail and/or phone for eligibility screening. A total of 457 controls were ineligible: 409 were too young, 44 were terminally ill, and 4 primarily resided outside of the study area. Of the 755 eligible population controls, 409 (54%) declined participation, were too ill to honor an appointment, or moved out of the area prior to interview: 346 (46%) were enrolled, and 162 of these persons were males aged 60-74 years and were included in this analysis (Table 2).

Exposure to chemicals with a potential role in prostate carcinogenesis

We provide results only for the most accurate exposure metric, based on residential locations between 1974 and 1999, when PUR and PLSS data were both available (Table 3). Results for exposures incurred prior to 15 years before diagnosis, exposures incurred prior to 10 years before diagnosis, and residence at diagnosis are presented in the text below only where they differed from the 1974-1999 exposure results. For 23 cases, there were no available exposure data because no usable residential history for any year of the period 1974-1999 could be obtained. These 23 cases did not differ from the remaining 150 according to any of the variables presented in Table 1, and their diagnosisaddress pesticide exposures appeared to be similar to those occurring among the 150 included cases. Only 12 participants had 1 or more years of missing address information

Table 3. Associations Between Prostate Cancer Risk and Exposure^a to Selected Pesticides, California's Central Valley, 2005–2006^b

Exposure	No. of Cases	No. of Controls	Odds Ratio ^c	95% Confidence Interval	P Value (High vs. Low)
Methyl bromide					
Missing data ^d	23	7			
Unexposed	63	85	1.00		
Exposed	87	70	1.62	1.02, 2.59	
Low exposure	45	35	1.81	1.03, 3.18	0.10
High exposure	42	35	1.45	0.82, 2.57	
Organochlorines ^e					
Missing data	23	7			
Unexposed	55	78	1.00		
Exposed	95	77	1.64	1.02, 2.63	
Low exposure	35	38	1.25	0.75, 2.08	0.037
High exposure	60	39	2.03	1.17, 3.52	
Captan					
Missing data	23	7			
Unexposed	92	104	1.00		
Exposed	58	51	1.20	0.74, 1.96	
Low exposure	17	25	0.68	0.34, 1.36	0.04
High exposure	41	26	1.74	1.01, 3.13	
Simazine					
Missing data	23	7			
Unexposed	82	87	1.00		
Exposed	68	68	0.96	0.60, 1.53	
Low exposure	30	34	0.84	0.47, 1.52	0.79
High exposure	38	34	1.07	0.60, 1.89	
Maneb					
Missing data	23	7			
Unexposed	118	121	1.00		
Exposed	32	34	0.85	0.48, 1.51	
Low exposure	14	17	0.71	0.32, 1.57	0.70
High exposure	18	17	1.00	0.47, 2.09	
Paraquat dichloride					
Missing data	23	7			
Unexposed	47	62	1.00		
Exposed	103	93	1.42	0.87, 2.31	
Low exposure	49	46	1.37	0.78, 2.41	0.37
High exposure	54	47	1.47	0.82, 2.60	

^a Based on historical exposures at reported residences between 1974 and 1999.

during the 1974–1999 period (representing 0.5% of the person-years of exposure data, because most were missing only 1 year); 98 participants spent 1 or more years out-of-county during the 1974–1999 period (1.96% of the person-years of exposure data, again because most were out-of-county for

only 1 year), and these were the participant-years for which exposures were imputed. Excluding any of these observations did not affect the results presented below.

Exposure to methyl bromide was associated with an increased risk of prostate cancer (odds ratio (OR) = 1.62, 95%

^b Results are based on California Pesticide Use Reports and address data for 1974–1999.

^c Adjusted for age, race/ethnicity, home pesticide use (yes/no), and occupational pesticide exposure (none, possible, or probable); see text for details.

^d There were no exposure data for missing observations for the period 1974–1999 (n = 23).

^e Dicofol, dieldrin, dienochlor, endosulfan, heptachlor, lindane, methoxychlor, and toxaphene.

Table 4. Associations Between Prostate Cancer Risk and Exposure to Selected Pesticides in the Underlying Population in California's Central Valley As Compared With the Study Sample, Using Only Diagnosis Address (Cases) and Recruitment Address (Controls)^a, 2005–2006

Exposure and Sample	Total No.	No. Exposed	% Exposed	Data Source	Odds Ratio	95% Confidence Interval
Methyl bromide						
Population controls	1,212	659	54.3			
Sample controls	162	73	45.1			
Population cases	670	406	60.6	Population	1.47	1.22, 1.78
Sample cases	173	92	53.1	Sample	1.44	0.93, 2.22
Organochlorines ^b						
Population controls	1,212	764	63.0			
Sample controls	162	84	51.9			
Population cases	670	459	68.5	Population	1.50	1.23, 1.83
Sample cases	173	117	67.6	Sample	2.05	1.31, 3.21
Captan						
Population controls	1,212	392	32.3			
Sample controls	162	51	31.5			
Population cases	670	322	48.1	Population	2.12	1.75, 2.57
Sample cases	173	68	39.3	Sample	1.45	0.92, 2.28

a Exposures were determined for all selected cases and controls, only from the diagnosis address in cases and the address used for recruitment for potential controls; see text for details.

confidence interval (CI): 1.02, 2.59), but we did not observe evidence for exposure-response (Table 3). Methyl bromide exposures at the diagnosis address were associated with a higher risk of prostate cancer (OR = 3.60, 95% CI: 1.62, 8.20) than any of the other periodic exposures, and there was evidence of exposure-response (for "low" exposure, OR = 2.75; for "high" exposure, OR = 4.01; P = 0.009 for the difference). Exposure to the group of organochlorines was associated with an overall increase in risk (OR = 1.64, 95% CI: 1.02, 2.63; Table 3), and there was substantial evidence for exposure-response, with a stronger risk increase in the "high" exposure category (OR = 2.03, 95% CI: 1.17, 3.52). Exposure to captan showed little difference in the comparison of unexposed and exposed groups (OR = 1.20, 95% CI: 0.74, 1.96) but elevated risk at high levels of exposure (OR = 1.74, 95% CI: 1.01, 3.13), with a statistically significant exposure-response trend (P-trend = 0.04). None of the estimates for captan, the organochlorines, or methyl bromide restricted to the periods 10 and 15 years prior to diagnosis varied significantly from those based on the 1974–1999 exposure period reported above.

Exposure to chemicals considered unlikely to be related to prostate carcinogenesis

We observed a slightly increased risk of prostate cancer at the highest level of simazine exposure, but the 95% confidence interval included the null value. Exposure to paraquat showed some evidence of a small increase in risk, but that increase was compatible with chance (Table 3). Any exposure to paraquat (based on residence of diagnosis only) increased the risk of prostate cancer (OR = 2.04, 95% CI: 1.10, 3.78), but the exposure-response pattern was inconsistent:

Higher risk occurred at low levels of exposure (low exposure: OR = 3.78; high exposure: OR = 1.84). Exposure to maneb did not appear to be related to increased risk of prostate cancer for any of the exposure metrics.

Assessment of selection bias

Using the limited exposure data available on all selected cases and controls (regardless of participation status), we found that pesticide exposures in participating study subjects were likely to be slightly underestimated (Table 4). Some odds ratios appeared to be affected by sample selection bias, but the direction and magnitude of the bias depended on the agent: For the group of organochlorines, the odds ratio in the case-control sample was 2.05, whereas the odds ratio in the underlying population was only 1.50, an estimate closer to the value of 1.64 based on address history in our sample (Table 3). The odds ratio for captan changed in the opposite direction, and the methyl bromide estimate appeared to be relatively unaffected by selection bias (Table 4).

DISCUSSION

In this population-based case-control study, we found evidence of a strong association of ambient exposure to methyl bromide and a group of organochlorines with prostate cancer risk. We tested only selected pesticides based on a priori hypotheses, and we found some evidence that the effects were limited to those compounds or chemicals most likely to be involved in prostate cancer initiation and promotion (methyl bromide, captan, and the group of organochlorines), with little evidence of a consistent effect for a selection of

b Dicofol, dieldrin, dienochlor, endosulfan, heptachlor, lindane, methoxychlor, and toxaphene.

compounds that are widely used but not thought to have a biologically plausible role in prostate cancer (paraquat dichloride, simazine, and maneb). Some of the associations observed were quite substantial, with the group of organochlorines showing over a 2-fold increase in risk of prostate cancer at higher exposure, albeit this estimate had relatively wide confidence intervals (OR = 2.03, 95% CI: 1.17, 3.52).

To our knowledge, no previous studies of prostate cancer and nonoccupational exposure to pesticides have been conducted in areas of such high potential exposure. California is the most productive agricultural state in the nation, with an annual production each year of more than 20 billion dollars' worth of different crops and commodities. Each year, the use of pesticides for agricultural purposes in California exceeds 250 million pounds of active ingredients, about one-quarter of all pesticides used in the United States. Fresno, Kern, and Tulare counties are ranked as the top agricultural counties in California by value of production (32), increasing the possibility of residential ("ambient") exposures' occurring via aerial drift of pesticides into neighborhoods and contamination of drinking water (33, 34). While the prevalence of residential exposure may be very high, studies have shown that acute exposure levels are probably relatively low; however, they are likely to accumulate substantially over a lifetime (35).

The most important recent data supporting a role of agricultural exposures in prostate cancer come from the Agricultural Health Study, in which Alavanja et al. (15) reported statistically significant relative risk estimates of approximately 1.3 for any pesticide exposure, but that study did not assess agricultural exposures other than occupational ones (such as residential exposure among persons living in agricultural areas) and may have provided poorer estimates of longer-term exposure (relying on accurate recall). Recently, Greenburg et al. (36) did not find any association between captan and prostate cancer in the Agricultural Health Study (odds ratios across quartiles were 1.00, 1.13, 0.82, and 1.02; none were significant), but it is difficult to compare that finding with our results, which deal with residential exposure in the general population rather than in specific occupational groups. While we might expect that any true associations between pesticide exposures and disease outcome would be especially high in occupationally exposed persons, selection bias (the healthy worker effect), exposure misclassification (e.g., recall bias), and real differences in exposure levels (e.g., if pesticide workers use effective exposure remediation methods) could all produce substantial differences in observed odds ratios between occupational and nonoccupational studies.

In this study, we considered exposures occurring in the general population, not a specific occupationally exposed cohort. This had the advantage that results were not biased by the healthy worker effect and could address the impact of ubiquitous pesticide exposures occurring in the general population. Estimation of exposure did not rely on recall of pesticide use. The validity of our PUR plus land-use GIS model in estimating potential residential exposures from pesticide applications to nearby agricultural crops (37) was previously examined: Using lipid-adjusted dichlorodiphenyldichloroethane (DDE) serum levels as the "gold

standard" for pesticide exposure, GIS-based organochlorine estimates had high specificity (87%), and together with body mass index, age, gender, mixing and loading pesticides by hand, and using pesticides in the home, they explained 47% of the variance in serum DDE levels (37). Adjustment (albeit somewhat crude) in the current study included occupational exposure to pesticides and home pesticide use, along with other potential confounders of the association between pesticide exposures and prostate cancer.

We also assessed the potential impact of selection bias for exposures in this case-control study. Ordinarily, this is not possible because the exposures in nonresponding survey or study subjects are unknown. There was some suggestion of bias in our pesticide exposure estimates; however, the direction of this bias was unpredictable, and the overall effects of specific pesticides on prostate cancer remained. Underestimation of pesticide exposures among control subjects in the worst case resulted in overestimation of the effect of any organochlorine exposure by 50% (in the participating subjects, OR = 2.05, 95% CI: 1.31, 3.21; in the underlying population, OR = 1.50, 95% CI: 1.23, 1.83), but it also resulted in underestimation of exposures for cases, such that for captan, the odds ratio in the selected cases and controls was 2.12 (95% CI: 1.75, 2.57). While the response rate in our study was relatively low, it is comparable to the rates commonly found in population-based casecontrol studies, and the cases included in this study were a relatively unbiased sample of the population-based series from which they were drawn with respect to demographic factors and the distribution of potentially confounding factors such as age.

Methyl bromide use has recently substantially declined in California because of international recognition that it is an ozone-depleting substance. The Environmental Protection Agency implemented a 100% phase-out plan scheduled for completion by 2005, but specially permitted use (where no practical alternative exists) continues (38). The grouping of organochlorines that we considered here consists of chemicals whose use is regulated (and must be reported) but is not limited in any manner that has affected their expanding use over time.

Clearly, this study would have benefited from an expanded sample size and a more detailed assessment of the relative importance of combinations of pesticides and of highly correlated pesticide exposures. While further improvements in exposure assessment and study design are undoubtedly warranted, we have demonstrated a method of pesticide exposure assessment that appears to minimize selection bias and exposure misclassification, resulting in fairly compelling evidence of measurable associations between prostate cancer and those pesticides with a biologically plausible mechanism in prostate carcinogenesis.

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Author affiliations: Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California (Myles Cockburn, Xinbo Zhang, John Zadnick); Spatial Sciences Institute, University of Southern California, Los Angeles, California (Myles Cockburn, Dan Goldberg); Department of Medicine, University of California, San Francisco, Fresno, California (Paul Mills); and Department of Epidemiology and Center for Occupational and Environmental Health, School of Public Health, University of California, Los Angeles, Los Angeles, California (Beate Ritz).

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